THE COUPLING OF HORMONE RECEPTORS AND ADENYLATE CYCLASE

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Receptors for many hormones and other transmitters, drugs, toxins, mitogens, and antigens are localized at the outer surface of the cell membrane. A major question is how combination of these diverse ligands with their receptors produce vast changes in the function and structure of target cells. The adenylate cyclase system present in plasma membranes of eukaryotic cells is a useful model for probing this question. This system is responsible for the transformations in cellular metabolism induced by numerous hormones, neurotransmitters, prostaglandins, and opiates. There is evidence that the adenylate cyclase system is composed of several types of subunits, including hormone receptors (R), catalytic unit (C) and nucleotide regulatory components (N) that selectively bind GTP. In the case of the glucagon-sensitive system in rat liver plasma membranes, a GTP regulatory unit (N_1), located at the inner face of the membrane, appears to be linked to the glucagon receptor at the outer face through proteins that span the lipid bilayer. This unit, designated RN_1, has a molecular weight of about 400,000 daltons and may be an oligomer of several subunits. Binding of the hormone to this unit in the absence of GTP results in a receptor conformation $(RN_1)_d$ in which the hormone remains tightly bound even when the unit is solubilized with detergents. Upon addition of GTP, this state is converted to two other states, one which binds with high affinity and which appears to be involved in activation by the hormone, and another which displays a lower affinity for the hormone $(RN_1)_s$. The catalytic unit of adenylate cyclase is associated with another GTP specific regulatory component, designated N_2, which binds GTP at sites which are structurally distinct from the N_1 site involved in receptor conformation. N_2C can be separated from the N_1R unit after detergent solubilization and is a large molecular weight unit (about 600,000 daltons). N_2C can be activated by GTP and non-hydrolyzable analogs such as $Gpp(NH)_p$ and $Gp(CH_2)_{pp}$, but not by hormone. Based on molecular weights estimated from high energy electron inactivation of the enzyme, GTP and hormone uniquely produce a molecular aggregate ($>10^6$ daltons) which is larger than either the N_2C or N_1R units. These data are consistent with the idea that both GTP and hormone, in concerted fashion, link RN_1 and N_2C to give a new oligomeric structure ($R\text{-}N_1\text{-}N_2\text{-}C$) that binds GTP and hormone with higher affinity than either of the units alone. The possibility is raised that N and N_2 are subunits of a protein (analogous to the subunits of tubulin) essential for uniting the disparate units of the adenylate cyclase system at the internal face of the membrane. The hormone receptor units may serve the function of promoting the interaction of the N-subunits through their linkage to the N_1 unit, thus providing for concerted integration of the molecular components of the system within the plane of the membrane. This model appears to apply to other membrane-bound adenylate cyclase systems and may have general applicability to problems of coupling of receptor and effector units within membranes, particularly where ligands acting at the extracellular surface influence the activity of units at the cytoplasmic surface of the cell membrane.